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BRIEF REPORT

Valproate-induced hyperammonaemic encephalopathy in a neonate: Treatment with carglumic acid☆

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Abstract Valproate-induced hyperammonaemic encephalopathy (VHE) is an unusual and serious complication of valproate (VA) treatment. When an early diagnosis is made, it can be reversed with VA withdrawal and early treatment for hyperammonaemia. We describe the case of a 20-day-old male, who developed a serious VHE after receiving VA for refractory neonatal seizures. The VHE was resolved with VA withdrawal in association with carglumic acid and other measures for hyperammonaemia treatment.

PALABRAS CLAVE
Valproico;
Hiperamoniemia;
Neonato;
Efecto adverso;
Ácido carglúmico

Encefalopatía hiperamoniémica inducida por ácido valproico en un neonato. Tratamiento con ácido carglúmico

Resumen La encefalopatía hiperamoniémica inducida por ácido valproico (EHV) es una entidad grave e inusual. Para su diagnóstico, precisa un elevado índice de sospecha, pues resulta reversible con la retirada del fármaco y el tratamiento precoz de la hiperamoniemia. Presentamos el caso de un neonato tratado con valproico (AV) por convulsiones refractarias, que desarrolló una EHV grave que revirtió con la retirada del AV y el tratamiento con ácido carglúmico, junto con otras medidas para control de la hiperamoniemia.

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Introduction

Valproic acid (VA) is an anticonvulsant that, while not being the first-line treatment for convulsions in neonates, is used as a second- or third-line treatment in Spain for convulsions refractory to phenobarbital treatment.[1] Valproate-induced hyperammonaemic encephalopathy (VHE) is rare (<1/10,000), but it is serious and potentially fatal.[2,3] The main physiopathological mechanism that leads to VHE is a gradual elevation of serum ammonia levels, leading to a clinical syndrome characterised by vomiting, progressive impairment of consciousness up to coma, focal neurological deficits, and increased seizure frequency.[4] There is no evidence that the incidence and severity of VHE are associated to blood VA levels, since in most published cases the levels were within therapeutic ranges, although there is evidence suggesting that anticonvulsant polytherapy (phenobarbital, phenytoin, and VA) may contribute to VHE.[5]

Treatment consists of discontinuation of VA and management of ammonia levels to prevent neurotoxicity, especially in neonates.[6] N-carbamylglutamate (NCG), also known as carglumic acid, is a synthetic analogue of N-acetylglutamate (NAG), one of the cofactors essential to the proper functioning of the urea cycle. NCG is indicated for treatment of hyperanaemia secondary to N-acetylglutamate-synthetase (NAGS) deficiency, although it has also been used to treat hyperanaemia of different aetiologies, such as VHE.[7]

We present the case of a neonate with VHE treated successfully with NCG and other measures against hyperammonaemia.

Clinical case

A male neonate, 20 days old, was admitted for a skull fracture and subdural haematoma secondary to occipital trauma, with no family history of metabolic disorders or consanguinity. He had been born at full term in a normal delivery and had an Apgar score of 9/10. The general examination at admission found a left parietal cephalohaematoma and neurological examination found only increased somnolence (Glasgow Coma Scale score 13/15). A computer tomography (CT) scan of the head revealed multiple diastatic skull fractures, extensive right subdural haematoma, and subgaleal fluid collections in the left parietal region (Fig. 1).

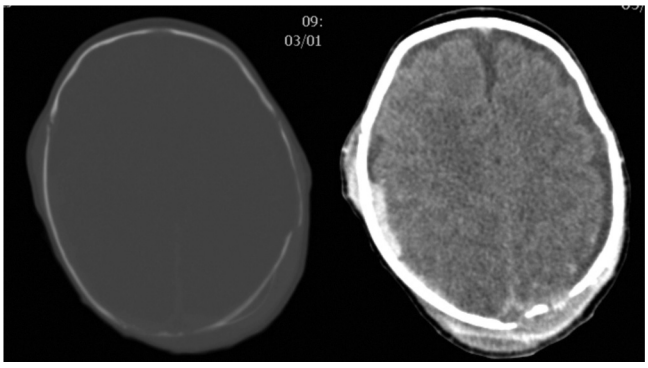

Figure 1 Multiple diastatic skull fractures, extensive right subdural haematoma, and subgaleal fluid collections in the left parietal region.

At 24 h after admission, he had partial seizures that were resolved with phenobarbital (initial bolus 20 mg/kg, maintenance 5 mg/kg/day) and midazolam. He had a new episode that consisted of a prolonged secondarily generalised partial seizure, so VA was added to the treatment regimen (initial bolus 15 mg/kg, maintenance 1 mg/kg/h). The electroencephalograph (EEG) at admission was normal, but after the seizures it detected focal activity in posterior regions of the right hemisphere that coincided with the location of the subdural haematoma (Fig. 2). At 48 h after initiation of VA therapy, the patient started showing signs of decreased level of consciousness, decreased spontaneous movement, and marked hypotonia and hyporeflexia. Examination did not reveal signs of intracranial pressure and a surveillance CT scan of the head did not show any changes. A new EEG showed generalised low-voltage slow activity compatible with cerebral oedema (Fig. 2B). Phenobarbital levels were normal and VA levels were slightly elevated (104.9 μg/mL). Basic laboratory testing (complete blood count, electrolyte panel, liver function) yielded normal results, and gasometry showed respiratory alkalosis. The serum ammonia level was 398 μmol/L. In light of these findings, treatment with VA was discontinued and treatment with carglumic acid (loading dose 100 mg/kg, maintenance 25 mg/kg/6 h orally) and carnitine (25 mg/kg/6 h orally) was initiated. Five hours later the level of ammonia had not decreased fast enough (374 μmol/L), so oral phenylbutyrate (125 mg/kg/6 h) and oral L-arginine (600 mg/kg/day) were added to the regimen. At 10 h, the ammonia level had dropped by half (182 μmol/L) and the VA level was within the normal range (69.8 μg/mL). At 18 h, the level of ammonia was normal (102 μmol/L) and the patient had improved considerably, so medication for hyperammonaemia was discontinued. A broad metabolic screening was done on a heel prick blood sample, the results of which were normal. The patient was monitored on an outpatient basis and evolved favourably. Phenobarbital treatment was discontinued at 4 months of age, and at age 1 year he showed normal psychomotor development, with no further episodes of convulsions.

Discussion

Although the treatment of neonatal convulsions has hardly changed in the past few decades, it remains a controversial subject because there are no evidence-based guidelines for their management. There is a general consensus that phenobarbital is the first-line treatment,[8] followed by phenytoin and benzodiazepines. Instances of treatment with other drugs, such as topiramate or levetiracetam, are starting to be published.[9] Valproate is also used as a second-line treatment after phenobarbital treatment failure with positive results, although it should be used with caution because there is limited experience in its use in neonatology.[1,10]

VHE is a rare and serious condition, especially in neonates. The main physiopathological mechanism involved is an increased serum ammonia level that causes an acute or subacute clinical presentation characterized by vomiting and decreasing level of consciousness that progresses towards coma and that may be associated to focal neurological deficits and increased seizure frequency.[4]